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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,832	03/30/2001	Thomas Tuschl	0399.2008-002	6240

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WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/821,832	TUSCHL ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-78,81,86-88,91,108,110,112,115-120 and 124-177* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-78,81,86-88,91,108,110,112,115-120 and 124-177* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/11/08 to the Non-Final Office Action mailed 10/31/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 10/31/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Also acknowledged are applicant's amendments to the claims. With entry of the amendment filed 3/11/08, claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 are pending and considered herein.

Non-Statutory Double Patenting

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 20-23, 76, and 80-85 of copending Application No. 10/255,568. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a method of mediating RNA interference of an mRNA in a cell comprising introducing into the cell double stranded RNA of from about 21 to about 23 nucleotides in length, and embodiments thereof wherein the mRNA is mammalian cellular mRNA.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

In an earlier Action, mailed 1/29/07, it was pointed out by the Examiner that:

1) MPEP §804, Section I, Part B.1 states in part that "If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue";

2) the conflicting applications are effectively filed on the same day. Thus, Application 10/255,568 is not a "later-filed" application;

3) a terminal disclaimer has not been required or voluntarily filed in conflicting application 10/255,568

4) the instant ODP rejection is not the only rejection remaining in the instant application; and that

5) the conflicting applications are not divisional applications of one another. The applications were not filed as the result of a restriction requirement in one or the other. The applications were voluntarily filed as separate applications. Thus, the prohibition against using the '568 Application as a reference against the instant application does not apply.

The instant rejection is proper therefor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30 and 34-55 of copending Application No. 11/142,866. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting application claims a method for chemically and enzymatically synthesizing nuclease resistant (i.e., stabilized) siRNAs of 19-25 nucleotides that mediate RNA interference. Absent convincing evidence to the contrary, the methods claimed therein would result in the production of dsRNAs having 3' hydroxyls.

One of skill would recognize that the methods for making dsRNA claimed in '866 could be used to make the dsRNAs now claimed in the instant application. Therefore, one of ordinary skill in the art would conclude that the products defined in the claims at issue are anticipated by, or would have been obvious in view of the methods for making defined in the claims in the conflicting application.

MPEP §804, Section I, Part B.1 states in part that "If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-

filed application before the ODP rejection can be withdrawn and the application permitted to issue."

Application No. 11/142,866 is a later filed application. However, a terminal disclaimer has not been required or voluntarily filed in conflicting application Application No. 11/142,866. Additionally, the instant ODP rejection is not the only rejection remaining in the instant application.

Therefore, the instant rejection is maintained.

***

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48, 49, 51, 53-57, 60-64, 67-73, and 75-125 of copending Application No. 10/433,050. Although the conflicting claims are not identical, they are not patentably distinct from each other because Application 10/433050 claims an isolated double stranded RNA molecule 19-23 nucleotides in length that mediates target-specific modifications of a mammalian gene.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

The instant rejections are not the only rejections remaining in the application and are therefore maintained. The conflicting applications have at least one common assignee and one common inventor, as acknowledged by Applicant in the Remarks filed 3/1//08. The common inventor would appear to be under obligation of assignment to the common assignee in each case. Unjustified timewise extension of patent rights to the same or obvious variant of the same invention would be obtained by at least the common inventor/assignee.

Nevertheless, with regard to the '050 and '866 applications above, the Examiner acknowledges that the instant application is the earlier filed application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 76–78, 81, 86–88, 91, 108, 110, 112, 115–120, and 124-177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crooke et al. (US Patent 6,107,094), as evidenced by Tuschl et al. (US 20040259247 A1) and Amarzguioui et al. (2003) *Nucleic Acids Res.* 31:589-595.

Tuschl et al. and Amarzguioui et al. are not relied on herein as prior art but only to show that a property is inherent (MPEP 2124 and 2131.01). See rejection below.

Crooke et al. taught double-stranded RNAs of 17 and 20 base-pairs in length for purifying and characterizing mammalian dsRNAses (cols. 46-58). Exemplary embodiments are set forth in Table 1, column 51. The double stranded RNAs used for such purposes comprise sense and antisense strands, wherein the antisense strand is 100% complementary to a mammalian mRNA such as Ha-Ras. The antisense strand is generally chemically modified such that an 8-9 ribonucleotide gap or core is flanked by one or more 2'-sugar modified and/or phosphorothioate modified nucleotides. See column 50, Example 27-a; column 52, lines 40-55; column 4, lines 15-30; columns 5-6; column 7, lines 20-30; column 11; and column 14, for example. Oligoribonucleotides modified in this manner are generally referred to therein as gapmers or chimeras.

It is said that the oligoribonucleotide gapmers, and i.e., impliedly, dsRNase substrates comprising said gapmers (i.e., dsRNAs), may be from about 5 to about 50 nucleotides in length,

or, more preferably, from about 15 to about 25 nucleoside subunits in length (col. 14, lines 10-20).

At column 8, lines 1-3, Crooke et al. expressly taught that part of their invention included useful substrates for dsRNases as well as affinity matrices comprising said substrates. In several working examples at columns 50-58, Crooke et al. taught that useful substrates for characterizing and purifying dsRNAes are dsRNAs of at least 17 and 20 base-pairs in length. In one method, it is taught the RNA affinity columns comprising said dsRNAs may be used to further purify dsRNases (column 53 and 55-58). Following purification, the dsRNase(s) may then be assayed using a double stranded RNA digestion assay, wherein dsRNA duplexes are incubated in an appropriate buffer containing the dsRNase(s). It is implied that various dsRNAs of various lengths in the recommended range (15-25 and 5 to 50) and with various flanking chemical modifications could be used in such an assay for characterizing dsRNase activity from almost any mammalian cell type.

At figure 4, Crooke et al. show dsRNase cleavage products may further be isolated and characterized in terms of their relative lengths to determine where and if cleavage has occurred in any given dsRNA duplex. See also figures 7 and 8 and Example 28-b, showing similar analyses.

Crooke et al. do not explicitly teach dsRNA gapmers of 21, 22, or 23 nucleotides in length.

However, in view of the disclosure cited above, stating that a preferred length for such substrates is 15-25 nucleotides in length or, more broadly, 5 to 50 nucleotides in length, teaching that dsRNA gapmers may be used to purify and characterize dsRNase activities from mammalian

cells, and showing that 17- and 20-nucleotide dsRNAs may be used for such purposes, it would have been obvious to one of skill that dsRNAs of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 nucleotides in length could each be used for the same purposes. That is, on the basis of the Crooke et al. disclosure, one of skill would have immediately envisioned chemically and non-chemically modified dsRNAs of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 nucleotides in length complementary to a mammalian gene (see Fig. 1, for example, showing an exemplary list of potential substrates). One of skill would have also reasonably predicted that each such substrate could be used in the applications exemplified therein for purifying and characterizing dsRNases. One of skill would have had reason to synthesize and use each dsRNase substrate of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 in length because Crooke et al. teach that dsRNAs of this length are substrates for dsRNase-catalyzed cleavage, and it would have been the normal desire of the scientist to further explore, expand upon, and understand the activities of mammalian dsRNases as taught by Crooke et al. One of skill would have further recognized that information gleaned from such studies would incidentally have been useful towards the optimization of the RNA gapmer method disclosed therein for targeted degradation of an mRNA via endogenous dsRNase activity, triggered by the introduction of an RNA gapmer, as taught by Crooke et al. (cols. 9-12, for example).

While Crooke et al. explicitly and implicitly taught the synthesis and use of dsRNAs (i.e., dsRNase substrates) of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 in length and complementary to a mammalian gene for the purification and characterization of dsRNases from mammalian cells, Crooke et al. do not teach the isolation of dsRNAs of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 in length obtained by cleavage of a dsRNA. However, Crooke et al. do

teach dsRNA digestion assays (col. 54, for example, but see 48-58) and the isolation of the digestion products by polyacrylamide gel electrophoresis (Figs. 4-8, for example; see also cols. 48-58). It is clear that if a dsRNA substrate of 25 to about 50 nucleotides in length were used in such an assay (50-nt substrates are implicitly suggested by the disclosure at column 14, lines 8-20, suggesting that 50-bp RNA-RNA duplexes are recognized by dsRNases), the resulting cleavage products would likely be on the order of 10-25 nucleotides in length, as evidenced by the cleavage mechanism shown in Fig. 4 Accordingly, one of skill practicing this assay with substrates in the range of 25 to 50-nts in length would necessarily isolate dsRNA cleavage products of between 21 and 23 nucleotides in length, meeting the limitations of the instant produc-by-process claims. For example, see claims 86-88, 91, and 142, as well as others.

While Crooke et al. do not teach that the dsRNAs intended for use as substrates for dsRNases, mediate RNA interference of a mammalian gene, Crooke et al. clearly taught that the single stranded RNA gapmers disclosed therein do mediate mRNA cleavage in a sequence specific manner, when introduced into a cell, via the formation of an RNA-RNA duplex. The disclosure teaches that this duplex is recognized by an endogenous dsRNase that then cleaves the duplex in the region of sequence complementarity. See Fig. 4., for example, but see entire disclosure.

Therefore, in view of such disclosure, and in view of the evidence in the art teaching that short interfering dsRNAs may be chemically modified at the 3' and/or 5' ends with one or more 2'-sugar or phosphorothioate modifications (see Tuschl et al., US 20040259247 A1, paragraphs 14-16), and in view of instant claims 110 and 112, for example, stating that the claimed double stranded RNA may comprise one or more non-standard nucleotides, there is sufficient reason to

believe the dsRNase substrates of 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 nucleotides in length and longer up to and including 50 nucleotides in length, taught by Crooke et al. would mediate RNAi of the gene to which they are targeted. As further evidenced by Tuschl et al., blunt-ended dsRNAs are RNAi-active (paragraph 9). As further evidenced by Amarzguioui et end-modified dsRNAs have RNAi activity. See Fig. 3 therein.

Thus, the product dsRNAs taught and suggested by Crooke et al. necessarily would mediate RNAi. Accordingly, because Crooke et al. disclosed products that are identical to those now claimed, Crooke et al. necessarily disclosed each of the biophysical and biochemical properties inherent to those products, including the RNAi properties recited in the instant claims (MPEP 2112 and 2145.II).

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

As Applicant knows, under the doctrine of inherency there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of*

invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Prior art made of record but not currently relied on

The following prior art is made of record and is not relied upon, but is considered pertinent to applicant's disclosure.

Livache et al. (US Patent 5,795,715) taught methods for making and using dsRNA of almost any length and sequence for diagnostic purposes.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
June 3, 2008